Cell Research

www.nature.com/cr
www.cell-research.com

RESEARCH HIGHLIGHT

Deadlier than the malate

Pingtao Ding[1], Hailong Guo[1] and Jonathan D. G. Jones[1]

Cell Research (2018) 28:609–610; https://doi.org/10.1038/s41422-018-0042-6

Plant and animal cells share similar malate-mediated cell death processes, but plants have evolved a unique intracellular communication between organelles in regulating programmed cell death in response to specific photoperiods.

Malate (malic acid) is made by all organisms. In plants, malate contributes to the pleasant taste in sour fruits. However, in a recent paper published in *Cell Research*, Zhao et al.[1] reported a novel role of malate in cell death of both plants and animals. It is the first report that the malate transfer from chloroplasts (the plant-specific photosynthetic organelle) to mitochondria can lead to cell death under continuous light.

Programmed cell death (PCD) in plants and animals plays an important role in development by eliminating unwanted cells and in response to environmental stimuli. Excessive elevation of intracellular levels of reactive oxygen species (ROS) can cause damage to lipids, proteins and DNA, known as oxidative stress, and induces PCD in both plants and animals. However, ROS can also serve as signaling molecules. ROS can be generated not only via cell surface NADPH oxidases but also in mitochondria (in both plants and animals) or chloroplasts (in plants).[2]

The same group reported previously that loss of function of MOD1 (mosaic death 1), a chloroplast-localized component of fatty acid synthase (FAS), leads to decreased enoyl-ACP reductase activity.[3] They further observed ROS accumulation in the FAS-deficient mutant *mod1*, which leads to premature cell death and altered morphology such as dwarfism in *Arabidopsis*.[4] To identify the components regulating cell death triggered by the dysfunction of MOD1, the authors screened for *mod1* suppressors and found mutations in genes encoding components of the mitochondrial electron transport chain (mETC) complex I.[4] These observations suggested that a signal might be transduced from chloroplasts to mitochondria.

To test this hypothesis, Zhao et al. screened for additional *mod1* suppressors with intact mETC complex I activities.[1] They reported new mutations in genes that encode a plastidial nicotinamide adenine dinucleotide (NAD)-dependent malate dehydrogenase (plNAD-MDH), a chloroplastic dicarboxylate transporter 1 (DiT1) and a mitochondrial malate dehydrogenase 1 (mMDH1). These proteins are all key components of the malate/oxaloacetate (OAA) shuttle in plants. Zhao et al. also confirmed that the impairment of fatty acid synthesis in *mod1* mutant can induce malate accumulation in chloroplasts, which subsequently causes oxidative stress in both chloroplasts and mitochondria.[1] The authors then verified that plNAD-MDH protein is localized in chloroplasts, the same as MOD1. DiT1 resides in the chloroplast envelope and one of its putative functions is to export malate from chloroplasts to the cytosol, whereas mMDH1 localizes to mitochondria. In *mod1* mutant, plNAD-MDH reduces OAA to malate in chloroplasts, and mMDH1 oxidizes malate to OAA in mitochondria. These processes couple with the conversion between NADH (NAD hydrogen) and NAD^+ (an oxidizing agent) and allow organelles in plants to communicate through the shuttling of malate to control ROS levels and redox status.[1]

Excess NADH in mitochondria can induce cell death and intracellular communication between different organelles is crucial for maintaining cellular homeostasis. The findings from Zhao et al. have shed light on how oxidative stress-derived signal (malate) shuttles from one organelle to another and causes cell death in plant cells. In addition, they showed that exogenous application of malate in a cultured human cell line can cause oxidative stress and cell death,[1] providing new evidence that malate may serve as a common redox signal of cell death in both plants and animals.

Malate can accumulate in chloroplasts where photosynthesis occurs and starch is stored. In *mod1-1* mutants, malate levels rise.[1] Excess malate exits the chloroplast and triggers cell death via mitochondria in a plNAD-MDH-, DiT1-, and mMDH1-dependent manner. This malate shuttling pathway may be especially important in maintaining a balanced redox status under continuous light.[1, 3, 4]

The malate signal comes from the chloroplast where reducing power is generated by photosynthetic reaction in a light-dependent manner. Malate relays this information into mitochondria where respiratory activity is sensitive to oxidative stress. Thus understanding how an irregular photoperiod leads to the MOD1-mediated cell death could provide new insights into delicate balance between energy production/utilization and redox homeostasis involved in the regulation of plant immune response.

Cell death occurs throughout plant life. Plants have evolved mechanisms to control cell death and avoid collateral damage. Cell death in plants can be either developmentally induced or triggered by environmental stresses, such as biotic and abiotic challenges. One well-known biotic stress-induced cell death is the hypersensitive response (HR), which is usually associated with activation of plant immunity.[2] Lesion mimic mutants, such as *lsd1*, can induce autoimmunity and HR in plants, which is enhanced by oxidative stress.[1] It is puzzling that proteins required for *mod1*-triggered cell death are not required for the cell death induced in lesion mimic mutant plants.[1] Another interesting observation by Zhao et al. is that cell death induced by *mod1* has a mosaic distribution in the leaf, whereas the lesion mimic mutants, such as *lsd1*, cause a runaway cell death.[1] One plausible explanation is that cell death caused by each mutant is propagated in different cell types, with distinct underlying mechanisms. In animals, different types of cells die in many different ways.[5] Therefore, it is crucial to investigate whether cell death in plants is cell-type specific and whether different mechanisms contribute to death in different cell types.

[1]The Sainsbury Laboratory, Norwich Research Park, Norwich NR4 7UH, UK
Correspondence: Pingtao Ding (pingtao.ding@tsl.ac.uk) or Jonathan D. G. Jones (jonathan.jones@tsl.ac.uk)

Published online: 29 May 2018

In addition, pathogen-induced HR has been shown to be influenced by photoperiod,[6] suggesting that some other unknown mechanisms in chloroplasts are involved, likely in addition to the malate pathway. Pathogen-induced HR in plants leads to systemic acquired resistance (SAR) and thus systemic immunity against a broad spectrum of pathogens.[7] A pipecolate pathway required for SAR has been identified recently.[8–10] Two enzymes involved in this metabolic pathway were shown to respond to the redox changes. In addition, products from this pathway can enhance pathogen-induced HR.[10] However, it is not clear how the activation of the pipecolate pathway potentiates cell death and how HR-associated redox changes might affect the enzymatic activities in this pathway. More detailed studies and comparisons between the cell death mediated by the malate pathway and the cell death enhanced by the pipecolate pathway will further reveal the mechanisms underlying different types of cell death in plants.

REFERENCES

1. Zhao, Y. et al. *Cell Res*. **28**, 448–461 (2018).
2. Van Breusegem, F. & Dat, J. F. *Plant. Physiol.* **141**, 384–390 (2006).
3. Mou, Z., He, Y., Dai, Y., Liu, X. & Li, J. *Plant. Cell.* **12**, 405–418 (2000).
4. Wu, J. et al. *Cell Res.* **25**, 621–633 (2015).
5. Nagata, S. & Tanaka, M. *Nat. Rev. Immunol.* **17**, 333–340 (2017).
6. Griebel, T. & Zeier, J. *Plant. Physiol.* **147**, 790–801 (2008).
7. Kombrink, E. & Schmelzer, E. *Eur. J. Plant Pathol.* **107**, 69–78 (2001).
8. Ding, P. et al. *Plant. Cell.* **28**, 2603–2615 (2016).
9. Hartmann, M. et al. *Cell*. https://doi.org/10.1016/j.cell.2018.02.049 (2018).
10. Chen, Y. C. et al. *BioRxiv*. https://doi.org/10.1101/288449 (2018).